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ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/769,034	KONDURI ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *6,28 and 52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-27 and 29-51* is/are rejected.

7)☒ Claim(s) *30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

1. Applicant timely traversed the restriction (election) requirement during a brief telephone interview on May 19, 2006 and in the reply filed on May 22, 2006. Applicant's election of the invention of Group I, Claims 1-52, the drug group corticosteroids and the drug species budesonide is acknowledged.

Applicant respectfully traverses the restriction requirement to elect one drug for examination purposes.

As stated in the Requirement for Restriction, the drugs are unrelated, as each is materially and structurally distinct, and confers distinctly different properties and effects on the target cell. Furthermore, each drug is independent and mutually exclusive of the others. A reference rendering a corticosteroid as anticipated or obvious over the prior art would not necessarily also render an antibiotic as anticipated or obvious over the prior art. Similarly, a finding that an antihistamine was novel and unobvious over the prior art would not necessarily extend to a finding that a serine lung protease inhibitor was also novel and unobvious over the prior art. Because these inventions are distinct for reasons given above, and because a search of one does not necessarily overlap with that of another, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes is made final.

2. As noted in the Requirement for Restriction letter, mailed May 2, 2006, Claim 28 is absent from the claim set. No amendment to the claims has been entered in response to the Requirement for Restriction, and thus Claim 28 is withdrawn from further consideration.

Claims 6 and 52 are pending, but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1-5, 7-27 and 29-51 are under consideration.

Priority

3. The Applicant's claim for priority under 35 U.S.C. 120 regarding the U.S. Provisional Application 60/498,609, filed on August 28, 2003 and U.S. Provisional Application 60/498,546, filed on August 28, 2003 is acknowledged.

Claim Objections

4. **Claim 28 is objected to because it is absent**. Applicant is reminded to renumber the claims accordingly.

Claim 30 is objected to because of the following informalities: the punctuation recited in the claim renders the three, chemically and structurally distinct phospholipids to become a single molecular compound. It appears that a conjunction is absent. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. **Claims 8 and 25 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 8 and 25 are self-referential and recite the term "the

carrier" and the limitations regarding the term "the polyethylene glycol". There is insufficient antecedent basis for the terms and the limitation in the claim.

6. **Claims 35-51 are rejected under 35 U.S.C. 112, first paragraph**, because the specification, while being enabling for a method for treating a respiratory tract of a mammal by aerosol administration of an effective amount of a composition comprising a sterically stabilized liposome carrier for combination with a drug, and a drug, the sterically stabilized liposome carrier consisting of phosphatidylglycerol (PG), phosphatidylcholine (PC), poly(ethylene glycol)-distearoylphosphatidylethanolamine (PEG-DSPE) and cholesterol (Chol) (PG:PC:PEG-DSPE:Chol) that is compatible with the respiratory tract of a mammal and effective to extend the effective life of the drug in the respiratory tract by a time equal to at least twice the effective life of the drug alone, does not reasonably provide enablement for all possible formulations and sterically stabilized liposomes component combinations that are compatible with the respiratory tract of a mammal and effective to extend the effective life of the drug in the respiratory tract by a time equal to at least twice the effective life of the drug alone. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the

state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

These claims are broad for encompassing a method of treating a respiratory tract of a mammal by aerosol administration of a large genus of liposome formulations of diverse component compositions. The inventive concept in the instant application is a sterically stabilized liposome whose structural properties yield the physiological property of being compatible with a mammalian respiratory tract, and via aerosol administration yield the pharmacological property of extending the effective life of the drug delivered in the respiratory tract by a time equal to at least twice the effective life of the drug alone in the respiratory tract.

These broad aspects are aspects that, given the nature of the invention, state of the prior art, and Applicant's disclosure, the Artisan would have to perform such experimentation as to essentially invent Applicant's subject matter.

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

The art has long recognized the existence of sterically stabilized liposome compositions, e.g. the formulation consisting of dicetylphosphate (DCP), phosphatidylcholine (PC), poly(ethylene glycol)-distearoylphosphatidylethanolamine (PEG-DSPE), and cholesterol (Chol) (DCP:PC:PEG-DSPE:Chol) (Deol et al, Biochimica et Biophysica Acta 1334: 161-172, 1997a), wherein the phospholipids used in liposome formulation, such as phosphatidylcholine and phosphatidylglycerol, may be derived from egg yolk or soybeans (Waldrep et al, U.S. Patent No. 5,958,378, column 5, lines 32-35, September 28, 1999). Similarly, Onyuksel et al (U.S. Patent No. 6,197,333 B1, March 6, 2001) teach a method to make sterically stabilized liposomes, also known as "PEG-liposomes", that are an improved drug delivery system of polymer-coated liposomes, wherein the polymer, such as PEG, is covalently conjugated to one of the phospholipids and provides a hydrophilic cloud outside the vesicle bilayer... allowing the sterically stabilized liposome to... increase the pharmacological efficacy of encapsulated agents (column 3, lines 20-45). One factor demonstrated to affect the circulation half-life of the

sterically stabilized liposome is that the PEG should have a molecular weight of approximately 2,000 Da, which is within the 500 to 5,000 Da range recited in Claim 8 of the instant application. According to Onyuksel et al, liposomes may be produced from combinations of lipid materials well-known and routinely used in the art to produce liposomes and including at least one lipid component covalently bonded to a water-soluble polymer (columns 7-8, joining paragraph). Lipids may include relatively rigid varieties, such as sphingomyelin, or fluid types, such as phospholipids having unsaturated acyl chains. Onyuksel et al teaches that polymers may include any compounds known and routinely used in the art of sterically stabilized liposome technology..., for example... PEG, preferred lipids such as PEG-DSPE, PC, and phosphatidylglycerol (PG), wherein the PC and PG may be egg-derived (column 14, lines 17-18) as recited in Claims 16 and 17 of the instant application, in further combination with cholesterol (Chol). It is noteworthy that one sterically stabilized liposome embodiment disclosed by Onyuksel et al is a liposome comprising the embodiment disclosed in the instant application, PG:PC:PEG-DSPE:Chol (column 8, lines 4-8; Example 2, column 14, lines 16-20), wherein the PC was present in an amount of 50%, the PG was present in the amount of 10%, and the PEG had a molecular weight of 2,000 Da, as disclosed by the composition limitations of the instant application. Thus, the level of one of ordinary skill in the art to manufacture sterically stabilized, or "stealth", liposomes is relatively high.

However, the art does not provide general guidance to demonstrate that sterically stabilized liposomes, such as the PG:PC:PEG-DSPE:Chol embodiment disclosed in the instant application and also taught by Onyuksel et al, can extend the life of a drug by two- to three-fold, as compared to free drug alone, in the respiratory tract of a mammal via aerosol delivery. The art teaches that stealth liposomes may be stable in the lungs for up to 4 days (the duration of the experiment), slow and control release of their encapsulated contents, e.g. isoniazid or rifampicin, and decrease the toxicity of the drug, compared to a non-encapsulated drug (Deol et al, Figures 3, 5 and 6, and Table 2). In particular, the cited references administered the stabilized liposomes by intravenous injection (in addition to Deol et al, 1997a and Onyuksel et al, 2001 above, see also Deol et al, June, Antimicrobial Agents and Chemotherapy 41(6): 1211-1214, 1997b and Zhang et al, Pharmaceutical Research 15(3): 455-460, 1998), and not by nebulization as taught in the instant specification. Furthermore, assays such as blood pressure (Zhang et al) or microbial

colony-forming units in the lung, liver or spleen (Deol et al, 1997b) were used to evaluate drug efficacy, as compared between free drug and stealth liposome delivery, and have not shown an at least two-fold extension of the effective life of the drug. Thus, at the time of the invention, considerable unpredictability in the art existed regarding the ability of a sterically stabilized liposome, even the PG:PC:PEG-DSPE:Chol embodiment disclosed in the instant application and also taught by Onyuksel et al, to extend the effective life of a drug in a mammalian respiratory tract by a time at least equal to twice that of free drug.

The Amount of Direction Provided by the Inventor and The Existence of Working Examples

The specification teaches that the inventive liposomes are "tailored to be compatible with naturally-occurring fluids found in the lung" so that the sterically stabilized liposomes provide long stability in the lungs (page 7, lines 20-25). However, the specification discloses a broad genus of compounds with which an artisan may use to create a liposome, many of which were already known in the art at the time of the invention, in particular the PG:PC:PEG-DSPE:Chol liposome component combination of the instant application (Onyuksel et al, column 8, lines 4-8; Example 2, column 14, lines 16-20). Furthermore, the specification does not teach several important considerations, such as the quantified, necessary amounts of each liposome component and their respective molar ratios such that the final liposome product will: a) be compatible with naturally-occurring fluids found in the lung so that the sterically stabilized liposomes provide long stability in the lungs, and importantly, b) extend the effective life of a drug in a mammalian respiratory tract by a time at least equal to twice that of free drug (pages 7-8, joining paragraph). Rather, the only example of a sterically stabilized liposome provided in the specification to extend the effective life of a drug in a mammalian respiratory tract by a time at least equal to twice that of free drug is a sterically stabilized liposome whose structural composition was previously disclosed by Onyuksel et al consisting of PG:PC:PEG-DSPE:Chol. Yet, the respective molar ratios of each component of this exemplified PG:PC:PEG-DSPE:Chol liposome that distinguish this liposome from the prior art and make manifest the property of extending the effective life of a drug in a mammalian respiratory tract by a time at least equal to twice that of free drug are not disclosed in the instant application.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Thus, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create an undue burden for a person of ordinary skill in the art to demonstrate that a liposome consisting of any one of all possible combinations of liposome components disclosed in the instant specification will yield a sterically stabilized liposome to extend the effective life of a drug in a mammalian respiratory tract by a time at least equal to twice that of free drug.

In conclusion, the specification fails to provide any guidance as to how an artisan would have dealt with the art-recognized limitations of the claimed product and method commensurate with the scope of the claimed invention and therefore, limiting the claimed invention to a method for treating a respiratory tract of a mammal by aerosol administration of an effective amount of a composition comprising a sterically stabilized liposome carrier for combination with a drug, and a drug, the sterically stabilized liposome carrier consisting of phosphatidylglycerol (PG), phosphatidylcholine (PC), poly(ethylene glycol)-distearoylphosphatidylethanolamine (PEG-DSPE) and cholesterol (Chol) (PG:PC:PEG-DSPE:Chol) that is compatible with the respiratory tract of a mammal and effective to extend the effective life of the drug in the respiratory tract by a time equal to at least twice the effective life of the drug alone, is proper.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. **Claims 1-4, 7-14, 16-27, 29-31, 33-34 are rejected under 35 U.S.C. 102(b),** as being anticipated by Onyuksel et al (U.S. Patent No. 6,197,333 B1, March 6, 2001).

The claims are drawn to a composition comprising a sterically stabilized liposome carrier for, and in, combination with a drug.

Onyuksel et al teach a method to make sterically stabilized liposomes, also known as "PEG-liposomes" and "stealth liposomes" that are an improved drug delivery system of polymer-coated liposomes, wherein the polymer, such as PEG, is covalently conjugated to one of the phospholipids and provides a hydrophilic cloud outside the vesicle bilayer... allowing the sterically stabilized liposome to... increase the pharmacological efficacy of encapsulated agents (column 3, lines 20-45). According to Onyuksel et al, liposomes may be produced from combinations of lipid materials well-known and routinely used in the art to produce liposomes and including at least one lipid component covalently bonded to a water-soluble polymer (columns 7-8, joining paragraph). Lipids may include relatively rigid varieties, such as sphingomyelin, or fluid types, such as phospholipids having unsaturated acyl chains.

With respect to the limitations of Claims 1-2, 14, 18-19 and 31, Onyuksel et al teaches that the liposomes produced according to the methods of the invention are characterized by improved stability and biological activity and are useful in a variety of therapeutic... applications, such as asthma, and may be delivered by aerosol administration, nebulization, inhalation, insufflation, or intratracheally (column 8, lines 7-10, 31 and 44-49).

With respect to the limitations of Claims 3-4, 9-12, 16-17, 20-23 and 33-34, Onyuksel et al discloses that polymers may include any compounds known and routinely used in the art of sterically stabilized liposome technology..., for example... PEG, preferred lipids such as PEG-DSPE, PC, and PG, wherein the PC and PG may be egg-derived (column 14, lines 17-18) as recited in Claims 16 and 17 of the instant application, in further combination with Chol.

With respect to the limitations of Claims 7-8, 24-27 and 29 Onyuksel et al discloses that one factor demonstrated to affect the circulation half-life of the sterically stabilized liposome is that the PEG should have a molecular weight of approximately 2,000 Da, which is within the 500 to 5,000 Da range recited in Claim 8 of the instant application.

With respect to the limitations of Claims 13 and 30, Onyuksel et al discloses a liposome structural composition embodiment also disclosed in the instant application, that is PG:PC:PEG-

DSPE:Chol (column 8, lines 4-8; Example 2, column 14, lines 16-20), wherein the PC was present in an amount of 50%, the PG was present in the amount of 10%, and the PEG had a molecular weight of 2,000 Da, as disclosed by the composition limitations of the instant application.

The specification of the instant application teaches that the inventive liposomes are "tailored to be compatible with naturally-occurring fluids found in the lung" so that the sterically stabilized liposomes provide long stability in the lungs (page 7, lines 20-25). However, the specification does not teach several important considerations, such as the quantified, necessary amounts of each liposome component and their respective molar ratios such that the final liposome product will: a) be compatible with naturally-occurring fluids found in the lung so that the sterically stabilized liposomes provide long stability in the lungs, and importantly, b) extend the effective life of a drug in a mammalian respiratory tract by a time at least equal to twice that of free drug (pages 7-8, joining paragraph). Rather, the only example of a sterically stabilized liposome to extend the effective life of a drug in a mammalian respiratory tract by a time at least equal to twice that of free drug provided in the specification is a sterically stabilized liposome consisting of PG:PC:PEG-DSPE:Chol, wherein the respective molar ratios of each component are not disclosed. Onyuksel et al did not administer their exemplative PG:PC:PEG-DSPE:Chol liposome by aerosol administration, and thus are silent with respect to the physiological and pharmaceutical properties of their liposome as ascribed by the instant application to be compatible with a mammalian respiratory tract or extend the effective life of a drug in a mammalian respiratory tract by a time at least equal to twice that of free drug. However, given that the liposome of Onyuksel et al is structurally the same as disclosed in the instant application, the liposome of Onyuksel et al would have inherently had the properties recited in Claims 1-2, 12, 14, 18-19, 29 and 31, that is a sterically stabilized liposome compatible with the respiratory tract of a mammal and effective to extend the effective life of a drug in a mammalian respiratory tract by a time at least equal to twice that of free drug alone, had it been delivered to the mammal by aerosol administration, a means contemplated by Onyuksel et al (column 8, lines 7-10, 31 and 44-49).

Thus, the invention(s) described by Claims 1-4, 7-14, 16-27, 29-31, 33-34 are anticipated by Onyuksel et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. **Claims 1, 5, 14-15, 18, 31-32, and 35-51 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Waldrep et al., U.S. Patent No. 5,958,378 (September 28, 1999) as applied to the limitation of a liposome carrier and the drug budesonide, and in further view of Onyuksel et al (U.S. Patent No. 6,197,333 B1, March 6, 2001) and as applied respectively to the limitations of a sterically stabilized liposome compatible with the respiratory tract of a mammal and a drug, as evidenced by Konduri et al (J. Allergy Clin Immunology, Supplement, 107(2): S315, 2001) and Waldrep (Abstract only, Drugs Today 34(6): 549-561, 1998).

The claims are drawn to:

a) a sterically stabilized liposome carrier for combination with a drug, the elected drug being budesonide,

b) a composition comprising a sterically stabilized liposome carrier in combination with a drug, the elected drug being budesonide, and

c) method for treating a respiratory tract of a mammal by aerosol administration of an effective amount of a composition comprising a sterically stabilized liposome carrier for combination with a drug, and the elected drug being budesonide, the sterically stabilized liposome carrier consisting of phosphatidylglycerol (PG), phosphatidylcholine (PC), poly(ethylene glycol)-distearoylphosphatidylethanolamine (PEG-DSPE) and cholesterol (Chol)

(PG:PC:PEG-DSPE:Chol) that is compatible with the respiratory tract of a mammal and effective to extend the effective life of the drug in the respiratory tract by a time equal to at least twice the effective life of the drug alone, as enabled by the instant specification.

Waldrep et al (U.S. Patent No. 5,958,378) taught a pharmaceutical aerosol composition comprising a single component phospholipid-containing liposome and budesonide, formulated for and delivered to mice by aerosol administration (column 10, Example 9). Waldrep et al do not teach a sterically stabilized liposome; however, at the time of the invention, Onyuksel et al taught a sterically stabilized liposome carrier in combination with a biologically active compound, wherein the liposome formulation comprises a combination of lipids and cholesterol, such as PG:PC:PEG-DSPE:Chol (column 8, lines 4-8) -a liposome composition that fulfills the liposome composition requirements recited in Claims 20-27, 29-30 and 36-46 of the instant application and wherein the sterically stabilized liposome is useful in a variety of therapeutic... applications, such as asthma, and may be delivered by aerosol administration, nebulization, inhalation, insufflation, or intratracheally (column 8, lines 7-10, 31 and 44-49). Onyuksel et al do not teach the biologically active compound carried by their respective sterically stabilized liposomes to be budesonide; however, at the time of the invention, Konduri et al taught a sterically-stabilized liposome in combination with the drug budesonide for the treatment of mice in an experimental asthma model. The abstract of Konduri et al does not explicitly describe the structural composition of the "sterically-stabilized liposome". However, the art recognizes that the term "sterically stabilized liposomes", also known as "PEG-liposomes" and "stealth liposomes", are an improved drug delivery system which has significantly minimized the occurrence of rapid clearance of liposomes from circulation (Onyuksel et al, column 3, lines 20-45, and references therein). Also, although Konduri et al do not explicitly state that the sterically stabilized liposome used in their study is "compatible with a mammalian respiratory tract", a person of ordinary skill in the art would reasonably conclude that the authors would purposefully choose a sterically stabilized liposome, as defined in the art-recognized terminology, that would in fact be compatible with a mammalian respiratory tract because the hypothesis tested by the authors was that "the administration of budesonide, when encapsulated in a sterically stabilized liposome, will prevent the inflammation of asthma in lower doses, given at less frequent intervals

compared to conventional therapy" (lines 10-13) and choosing a sterically stabilized liposome that was *not* (*emphasis added*) "compatible with a mammalian respiratory tract" would be antithetical to their purpose, especially in light of the state of the art published at least three years earlier demonstrating the existence of sterically stabilized liposomes compatible with the respiratory tract of a mammal.

It would have been obvious to one of ordinary skill in the art to modify the single component liposome carrier of Waldrep et al with a sterically stabilized liposome composition as taught by Onyuksel et al with a reasonable chance of success because Onyuksel et al demonstrate the successful formulation of a sterically stabilized liposome in combination with a drug that may be administered by aerosol delivery to a mammalian respiratory tract. An artisan would have been motivated to modify a liposome carrier into a sterically stabilized liposome because Onyuksel et al teach that "numerous modifications and variations in the invention... are *expected to occur* (*emphasis added*) to those skilled in the art" (column 20, lines 54-57). Similarly, Waldrep (Abstract, 1998) teaches that there is "a conspicuous lack of suitable formulations" and that "the utilization of liposomes for aerosol delivery has many potential advantages, including universal carrier suitability for most...drugs".

It would have been obvious to one of ordinary skill in the art to substitute the biologically active compounds taught by Onyuksel et al with budesonide, as taught by Waldrep et al and Konduri et al with a reasonable chance of success because Waldrep et al successfully demonstrated that budesonide can be delivered to mammalian respiratory tracts using an aerosol liposome and Konduri et al successfully demonstrated that budesonide administered by a sterically stabilized liposome significantly decreased lung inflammation. An artisan would be motivated to use budesonide for the treatment of a respiratory tract because Waldrep (Abstract, 1998) teaches that "drug liposome aerosol technology represents one readily available approach for more effective therapeutic intervention in the lung using ... budesonide". And furthermore, several structurally similar glucocorticoids, i.e. budesonide, have been available for aerosol treatment of said diseases (Waldrep et al, columns 1-2, joining paragraph).

Therefore, the invention(s) was *prima facie* obvious.

9. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DAVE TRONG NGUYEN
SUPERVISORY PATENT EXAMINER